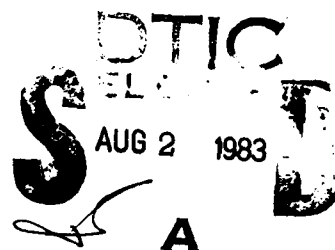


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## Subeschar Treatment of Burn-Wound Infection

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• Within a 24-month period, 454 patients were admitted with burns (average size, 33% of the total body surface [TBS]). Wound infection developed in 19, who subsequently were treated with subeschar antibiotics. The average burn size in those 19 patients was 63% of the TBS, with an average full-thickness injury of 47%. Five (26%) of the 19 survived, and five others died without evidence of wound infection, giving a wound clearance rate of 52.6%. The five surviving patients (average burn size, 59% TBS) underwent excision of infected tissue, with split-thickness cutaneous autograft closure of the burn wound, after the course of subeschar antibiotic infusion. All surviving patients were infected with *Pseudomonas aeruginosa*. Subeschar infusion of semisynthetic penicillins, therefore, is an effective adjunct in the care of the patient with *Pseudomonas* burn-wound infection.

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biotic treatment of histologically confirmed burn-wound infection.

### PATIENTS AND METHODS

During the 24-month period from January 1980 through December 1981, 454 patients with burns were admitted to the US Army Institute of Surgical Research. The average burn size was 33.2% of the total body surface (TBS); the range, 0.5% to 100%. One hundred forty-three patients (31.5%) had suffered inhalation injury, a diagnosis established by some combination of history, physical examination, flexible fiberoptic bronchoscopy, xenon Xe 133 ventilation-perfusion lung scanning, and pulmonary function tests. Two hundred eighty-nine patients (63.6%) were admitted within 48 hours of injury. Three hundred forty-eight patients (76.6%) were male, and 106 (23.4%) were female. The average age was 29 years; the range, 3 months to 92 years.

During the postburn hospital course, burn-wound infection caused by *Pseudomonas aeruginosa* developed in 19 patients (4.2%) and was treated by subeschar infiltration of the wound with a semisynthetic penicillin (carbenicillin disodium). Topical antimicrobial chemotherapy of the burn wound was also provided, using sequential applications of mafenide acetate cream during the day and sulfadiazine silver cream during the night. The wound was cleansed daily, by showering, when possible, in the Hubbard tank, or at the bedside. Prophylactic antibiotics were not administered systemically. Intravenous antibiotics were administered for infections diagnosed either clinically or on the basis of blood cultures, and the selection of antibiotics was initially based on the antibiotic sensitivity of the predominant microbial flora at our center and subsequently guided by culture and sensitivity reports and the patient's clinical response to therapy.

The diagnosis of burn-wound infection was confirmed by histologic examination of biopsy specimens of areas suspected of harboring infection.<sup>1</sup> Quantitative microbiologic techniques were used to determine the identity and density of the microorganisms. Once gram-negative-bacterial burn-wound infection was diagnosed, the topical application of sulfadiazine silver burn cream was discontinued, and the burn wound treated with mafenide acetate cream

Topical chemotherapy of the burn wound has reduced the incidence of burn-wound infection as a cause of death. However, patients continue to die of such infection; once generalized burn-wound sepsis has developed, the chance of survival is 10% or less.<sup>1</sup> Baxter et al originally proposed the subeschar administration of antibiotics as a treatment for the burn wound that becomes infected despite topical chemotherapy.<sup>2</sup> Subeschar clays offers the theoretical advantage of direct administration to an infected burn wound that may be inaccessible to intravenous (IV) antibiotics. We reviewed the recent experience of the US Army Institute of Surgical Research (San Antonio, Tex) with subeschar anti-

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Table 1.—Clinical Findings in Patients Treated With Subeschar Clysis

Age/Sex	Burn Size, % TBS*		Inhalation Injury	Organism in Initial Biopsy Specimen (No.)†	Posttreatment Biopsy Results	Outcome‡	Autopsy
	Total	Full					
23 yr/M	83.0	67.5	Yes	<i>Pseud</i> ( $1.5 \times 10^7$ )	Negative	D (Renal failure)	No
50 yr/M	26.0	17.0	Yes	<i>Pseud</i> ( $5.0 \times 10^6$ )	Positive	D (BWS)	Yes
13 yr/F	73.5	64.0	No	<i>Pseud</i> ( $3.0 \times 10^6$ )	Negative	D (Pneumonia)	Yes
38 yr/M	82.0	55.0	Yes	<i>Pseud</i> ( $8.0 \times 10^6$ )	Positive	D (BWS)	Yes
4 mo/M	34.0	...	No	<i>Pseud</i> ( $3.0 \times 10^6$ )	Negative	S	...
19 yr/M	78.5	72.5	No	<i>Pseud</i> (...)	Negative	D (Pneumonia)	Yes
30 yr/M	94.5	90.5	No	<i>Pseud</i> and <i>S aureus</i> ( $9.0 \times 10^7$ )	Positive	D (BWS)	Yes
32 yr/F	58.0	46.0	Yes	<i>Pseud</i> ( $8.0 \times 10^6$ )	Positive	D (BWS, pneumonia)	Yes
27 yr/M	54.0	48.0	Yes	<i>Pseud</i> ( $1.0 \times 10^6$ )	Positive	D (BWS, pneumonia)	Yes
31 yr/M	84.5	49.5	No	<i>Pseud</i> ( $1.0 \times 10^4$ )	Negative	D (Pneumonia)	Yes
40 yr/M	53.0	51.0	No	<i>Pseud</i> ( $1.0 \times 10^6$ )	Positive	D (BWS)	Yes
16 yr/F	56.5	24.5	No	<i>Pseud</i> ( $1.8 \times 10^7$ )	Positive	D (BWS)	No
26 yr/M	68.5	46.5	Yes	<i>Pseud</i> ( $1.0 \times 10^7$ )	Positive	D (BWS, pneumonia)	Yes
3 yr/M	50.5	3.0	No	<i>Pseud</i> ( $6.2 \times 10^7$ )	Positive	D (BWS)	No
19 yr/M	77.0	39.0	No	<i>Pseud</i> and <i>Prov</i> ( $2.0 \times 10^6$ )	Negative	D (Pneumonia)	No
21 yr/M	58.0	28.0	No	<i>Pseud</i> ( $3.0 \times 10^6$ )	Negative	S	...
22 yr/M	73.5	58.0	Yes	<i>Pseud</i> and <i>Prov</i> ( $3.4 \times 10^3$ )	Negative	S	...
16 yr/M	86.0	75.0	No	<i>Pseud</i> ( $1.0 \times 10^6$ )	Negative	S	...
36 yr/M	43.0	5.0	No	<i>Pseud</i> ( $1.8 \times 10^7$ )	Negative	S	...

\*TBS indicates total body surface; Full, full thickness.

†*Pseud* indicates *Pseudomonas*; *S*, *Staphylococcus*; and *Prov*, *Providencia stuartii*.

‡Causes of death are given parenthetically. D indicates death; S, survival; and BWS, burn-wound sepsis.

twice daily, reapplied as necessary to maintain adequate topical chemotherapy.

If the offending microorganism was a gram-negative bacillus, a semisynthetic penicillin (carbenicillin disodium) was injected into subeschar tissue beneath the infected burn wound. One half of the recommended daily dose of the antibiotic (based on body weight) was administered via subeschar clysis twice daily for two days or continued until the infection was controlled. The antibiotic was suspended in sufficient diluent to treat the entire infected burn wound, and a No. 20 spinal needle was used for the injections, to minimize the number of skin puncture sites.

### RESULTS

Nineteen patients were treated with subeschar injection of a semisynthetic penicillin (carbenicillin), after histologic confirmation of bacterial burn-wound infection (Table 1). The average burn size in those patients was 63% of the TBS, with an average full-thickness injury of 47% TBS. The average age was 24.3 years, and the range, 4 months to 50 years. Five of the 19 patients (26%) survived and were discharged from the hospital. The average burn size in the five survivors was 59% of the TBS (range, 34% to 86%), and the average age was 19 years (range, 4 months to 36 years). All surviving patients were infected with *P aeruginosa*. Only one of them had confirmed inhalation injury. After the course of antibiotic infusion, all five underwent wound debridement and burn-wound closure with split-thickness cutaneous autograft.

Five additional patients died without evidence of residual burn-wound infection. The absence of burn-wound infection was confirmed by postmortem examination in three, antemortem histologic examination of the excised burn wound in one, and a second biopsy of a previously infected burn wound in one. All five patients died of pulmonary complications, and one also had acute renal failure. Altogether, in 52.6% of patients (ten of 19) burn wound infection resolved after subeschar antibiotic therapy.

In seven of the other nine patients who died, residual burn-wound invasion was confirmed at autopsy. In addition, five of those seven had associated fungal burn-wound invasion, and two had uncontrolled dissemination of infection to remote organs. In the two patients for whom autopsy permission was not obtained, one died within 12 hours of the diagnosis of burn-wound infection, and residual infection was histologically confirmed before death in the other. Both of them had generalized burn-wound infection as well as disseminated infection.

### COMMENT

Patients in whom burn-wound infection is more likely to develop include extensively injured patients, ie, those with burns larger than 30% of the TBS, children, and patients with postburn complications that result in decreased blood flow to the burn wound. The 19 patients reported herein were extensively injured, with an average burn size of 63%

Table 2.—Classification of Burn-Wound Infection by Histologic Grade
I. Contamination (occasional organism on surface of wound)
II. Surface colonization (heavy growth limited to wound surface)
III. Partial penetration (organisms within eschar but not at deep margin)
IV. Complete penetration (organisms identified at deep margin of eschar)
V. Subeschar space infection (proliferation of microorganisms at viable-nonviable tissue interface)
VI. Invasive infection (microorganisms identified in viable tissue)
A. Focal microinvasion (early focus in viable tissue)
B. Multifocal or generalized invasion (extensive spread of microorganisms into viable tissue)
C. Microvascular involvement (organisms invading blood vessels, making hematogenous spread likely)

of the TBS and average full-thickness injury of 47% of the TBS, compared with the averages of 33.2% and 15.7%, respectively, for all patients admitted to the institute during the period of review. The age and sex distribution of the patients in whom burn-wound infection developed were not different from those of the entire inpatient population.

A diagnosis of burn-wound infection was suspected clinically when partial-thickness wounds converted to full-thickness necrosis, when a wound showed hemorrhagic or black discoloration, when early eschar separation occurred, when unburned skin at the margin of the burn wound became edematous with erythematous or violaceous discoloration, or when ecthyma gangrenosum developed. Histologic confirmation of burn-wound infection was accomplished in all 19 cases, using criteria previously described for the rapid diagnosis of burn-wound infection or invasion<sup>3</sup> (Table 2). Quantitative microbiologic evidence of proliferation of microorganisms in excess of  $10^5$  organisms per gram of tissue was considered indicative of burn-wound invasion, but not diagnostic. Cultures were helpful in identifying the causative organisms.

Once a diagnosis of bacterial burn-wound infection was established, an absorbable, topical chemotherapeutic agent, mafenide acetate burn cream, was applied continuously to the burn wound, IV antibiotic therapy and supportive treatment were instituted, and consideration was given to definitive wound treatment. If histologic examination of the burn wound supported the clinical impression of *Pseudomonas* burn-wound infection, subeschar clysis of the infected burn wound was performed, as already described. Repeated histologic examination of the infected wound to evaluate the effectiveness of treatment was done after the subeschar clysis, either at the time of operative excision of infected tissue or by biopsy of the burn wound after 48 hours of therapy. In interpreting burn-wound biopsy specimens after subeschar antibiotic therapy, one must bear in mind the fact that injection of the antibiotic solution may cause hemorrhage independent of infection.

After subeschar infiltrations with antibiotic solution, excision of infected tissue was considered. Excision was indicated when there was a need to remove full-thickness

Table 3.—Clinical Condition at Diagnosis of Burn-Wound Infection				
	Generalized Burn-Wound Infection	Positive Blood Culture	Acidosis Shock	Hyperglycemia
Survivors, No. (n = 5)	2	0	0	2
Patients who died without wound infection, No. (n = 5)	2	4	4	3
Patients who died with wound infection, No. (n = 9)	7	7	7	5

infected tissue because of extension of existing lesions, new foci of wound infection, dissemination to unburned tissue or remote organs, or persistent or worsening systemic sepsis. The decision to excise infected tissue was influenced by the blood loss associated with excision, the risk of septic shock, the anesthetic risk, and the general physiologic condition of the patient. Four of the five patients who died without evidence of residual wound infection did not undergo excision, because of associated pulmonary complications and the magnitude of their injuries (average burn size, 78.4% of the TBS; range 73.5% to 84.5%). In the fifth patient who died, whose burn covered 83% of the TBS, the infected tissue was excised, and the excised wounds were dressed with allograft from a cadaver. That patient died seven days after excision, of irreversible pulmonary and renal complications.

It is essential to provide immediate coverage of the excised wound, to minimize the risk of desiccation and reinfection. In the five surviving patients, three underwent wound excision at the level of the investing fascia, with immediate application of split-thickness cutaneous autografts, and two had biologic dressings (porcine xenografts or cadaver allografts) applied after the excision. In the latter two patients, the wounds were later closed with split-thickness cutaneous autografts, once there was no evidence of residual infection.

The magnitude of clinical infection and the incidence of blood cultures yielding *Pseudomonas aeruginosa* indicate that the nine patients who died with infected burn wounds had more severe infections than the five survivors (Table 3). No surviving patient had septicemia, despite histologic confirmation of bacterial burn-wound invasion. Thus, the subeschar infusion of antibiotics appears to be more effective before the development of disseminated sepsis, as would be expected.

In the absence of blood supply to burn eschar, nondiffusible, systemically administered antibiotics were shown to be ineffective in the treatment of burn-wound infection in a standard animal model.<sup>4</sup> Although others<sup>2</sup> have used various antibiotics for the subeschar treatment of burn-wound infection, recent laboratory studies at our institute demonstrated that such experimental burn-wound infections could

be treated with diffusible antibiotics given via intraperitoneal, subcutaneous, or subeschar routes. The effectiveness of the subeschar route of carbenicillin administration in that animal model was the basis for our treatment choice.

Nine of 593 patients treated during a two-year period before the use of subeschar antibiotic infusion required emergency excision of infected burn wounds to control bacterial burn-wound sepsis. The use of subeschar antibiotics has eliminated the necessity for such emergency excision in our center, permitting elective operation on patients who have received adequate preoperative antibiotics and supportive therapy, and thus minimizing the risk of septic shock during or after operation. On the basis of our limited

experience, the subeschar infusion of the semisynthetic penicillin carbenicillin appears to be an effective adjunct in the care of patients with focal and early, generalized, *Pseudomonas* burn-wound infection.

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## Discussion

CHARLES R. BAXTER, MD, Dallas: The authors are to be congratulated for the mortality that they obtained in this very ill group of patients and for demonstrating again the effectiveness of the subeschar technique as an adjunct to the treatment of burn-wound sepsis.

The subeschar technique is based on the original observations of Drs Order and Moncrief, demonstrating the ischemia within a burn wound and the failure of nutrients or treatment to get into the wound to attenuate bacterial colonization that invariably takes place in damaged or dead tissue, and the studies, beginning with that of Monasterio in Mexico in the early 1950s, showing that systemically effective antibiotics do not really affect the course of burn wounds.

The authors have added two innovations that are difficult to evaluate. They have applied the clysis twice-a-day, instead of once, and they have used synthetic penicillins, which we have not used to any great extent.

The eradication of almost 53% of the organisms from the wound is much better than our own experience with the technique. Whether this improvement is due to the use of synthetic penicillins or the twice-a-day technique is unclear.

When we used the synthetic penicillins in patients initially, we found that they produced a great deal of pain, which caused us to go back to using aminoglycosides and other specific antibiotics for the organisms cultured. Other antibiotics, such as erythromycin, are also very painful and are not used in subeschar infusion.

I think the treatment of established infections represents one of the applications of the subeschar technique. We are prone to use the subeschar technique much earlier in the course of burn-wound colonization. In a previous study, we found that when patients began to have colonization with increasing log concentrations, the incidence of invasive sepsis approached 70%. Not all patients with colonization have invasion (class V colonization or burn-wound invasion), but the majority of them do get sick.

Why not begin treatment earlier in this high-risk group, instead of waiting to see all the systemic signs that we associate with death?

CHARLES GILLON WARD, MD, Miami: In the group that the

authors thought was too sick to take to the operating room and excise their wounds, what were the final results? Our experience has been that this is a very tricky group of patients to treat. They may be the very ones that most need to go to the operating room, but one hesitates because of the difficulty in getting them there. However, if they have continuing sepsis from their burns, they do need their wounds excised.

JOHN F. BURKE, MD, Boston: Would Dr McManus tell us what he thinks would happen if excision were done before sepsis developed, rather than afterward?

DR McMANUS: In answer to Dr Burke's question, we have indications for early excision at the Institute of Surgical Research, and conservative or nonoperative care until the time of spontaneous eschar separation is generally not employed, unless serious associated injury or disease precludes early operative intervention. Those patients whose burn wounds were not excised had a contraindication to early excision. The contraindications include burns exceeding 60% of the TBS, confirmed inhalation injury, and age greater than 60 years, all of which have been shown in previous studies to lead to postoperative complications.

In answer to Dr Ward's questions, the patients who did not have wound excision after subeschar clysis had contraindications for operative intervention, such as uncontrolled metastatic infection, shock, or pneumonia.

To answer Dr Baxter, in a previously reported study of a laboratory animal model of reproducible burn-wound infection, we found that the only agents that protected these animals from death from burn-wound sepsis were the semisynthetic penicillins, such as carbenicillin. Despite in vitro sensitivity of the organisms to gentamicin, neomycin, or colistin, no reduction in mortality could be observed in this animal model with the subeschar use of those antibiotics.

Regarding the question about pain, we give the patient adequate IV analgesia to relieve pain, before the procedure.

As far as why we do not use subeschar clysis earlier, I have no data to suggest that that would not be of advantage, and I think the question is an interesting one.

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